REMARKS

The title of the application is amended as suggested by the Examiner.

Claims 67-68 have been amended to recite a method that includes the step of administering to an individual an effective amount of an NF-kB inhibitor, in combination with a substance that relieves skin irritation, an antimicrobial agent, and a thermal insulating material.

Support for the amendments is found throughout the specification and in the originally filed claims. No new matter is introduced.

The remainder of this Amendment is set forth under appropriate subheadings for the convenience of the Examiner.

Election/Restrictions Requirement

Applicant affirms the election of Group I (Claims 1-11, 14, 16-37, 40-51, 57-61, 67-74, 77-78).

Claims 67 and 68, presently in Group I, recite use of a cyclooxygenase or NF-kB inhibitor in combination with a substance that relieves skin irritation, an antimicrobial agent and a thermal insulating material. Applicant respectfully request, therefore, that Claims 67 and 68 be rejoined with the claims in Group III, specifically Claims 12-13, 15, 38-39, 62-66, 75-76 and 79.

Applicant reserves the right to file a continuing application or take such other appropriate action as deemed necessary to protect the non-elected invention of Group II (Claims 52-56) and of Group III (Claims 12-13, 15, 38-39, 62-66, 75-76 and 79, as well as Claims 67 and 68, discussed above). Applicant does not hereby abandon or waive any rights in the Groups II and III inventions.

The nonelected Claims 52-56 (Group II) and Claims 12-13, 15, 38-39, 62-66, 75-76, 79 (Group III) are being cancelled without prejudice to their reinstatement in this or a continuing application. & cont trav.

Specification

The Examiner required a new title of the invention.

Applicant has amended the title of the application to the title suggested by the Examiner. Specifically, the amended title reads: Methods for Improving the Size and Appearance of a Healed Wound.

Claim Rejections Under 35 U.S.C. §112

Claims 67 and 68 were rejected under 35 U.S.C. § 112, second paragraph. The Examiner stated that the claims do not set forth any steps involved in the method/process.

Applicant has amended Claims 67 and 68 to recite the step of administering to an individual in need thereof, a therapeutically effective amount of a cyclooxygenase or NF-kB inhibitor, in combination with a substance that relieves skin irritation, an antimicrobial agent, and a thermal insulating material.

As amended, Claims 67 and 68 comply with the requirements of 35 U.S.C. § 112, second paragraph.

Claim Rejections Under 35 U.S.C. §101

Claims 67 and 68 were rejected under 35 U.S.C. § 101. In the Office Action, the Examiner stated that the "claimed recitation of use, without setting forth any steps involved in the process results in an improper definition of a process."

Claims 67-68 are amended to recite the step of administering to an individual in need thereof, a therapeutically effective amount of a cyclooxygenase or NF-kB inhibitor, in combination with a substance that relieves skin irritation, an antimicrobial agent, and a thermal insulating material.

As amended, Claims 67-68 meet the requirements of 35 U.S.C. § 101.

Applicant's Invention

In one embodiment, Applicant's invention is related to the discovery that the size and appearance of a healed wound, such as a wound that is closed after an open wound has been reepithelialized, can be improved by administering at least one compound that directly or indirectly inhibits cyclooxygenase. As claimed, the embodiment is directed to a method for improving the size and appearance of a healed wound (e.g., a scar), comprising administering to

an individual in need thereof a therapeutically effective amount of a cyclooxygenase or NF-kB inhibitor. In addition to improving the size and appearance of a healed wound, the claimed method also results in reduced skin irritation and inhibition of excessive scar symptom in the healed wound. Page 6, line 9 to page 9, line 7 of the subject application.

Claim Rejections Under 35 U.S.C. 102

I. Claims 1-4, 8, 11, 27-30, 34, 37 and 67-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Sibley et al.

The Examiner stated that the reference "discloses salicylic acid formulations for treatment of keloids caused by acne" and that "the formulations also disclose inclusion of substances that relieve skin irritation." Office Action at page 6.

Applicant respectfully notes that the correct number of the cited patent document is DE 2707537, as shown on PTO-892 Form (Part of Paper No. 8), rather than DE 2107537, as indicated in the Office Action. An English language translation of document DE 2707537 ('737) is included with the Second Supplemental Information Disclosure Statement filed concurrently herewith as Reference AN2.

Applicant has not found the word "keloids" in the English translation of Sibley et al. and respectfully request the Examiner to point out, in either the original or in the English language translation, the text excerpt where the cited document discloses "keloids."

Sibley et al. disclose a thixotropic gel suitable for the local treatment or control of ongoing Acne vulgaris and other conditions brought about by infected sebaceous glands. Specifically, at page 7, fourth paragraph of the enclosed translation, Sibley et al. state:

> The preparation of the invention is a nontransparent gel, which can easily be applied onto the skin, with the formation of a transparent layer. The preparation serves for the treatment of sebaceous accumulations, pustules and papules, as they may occur in Acne vulgaris. With regular application, the formation of blackheads can be prevented. The preparation of the invention is also suitable for the treatment of tinea versicolor, seborrheic dermatitis, as well as other disorders, which are associated with

> hyperplasia that has been brought about by infected sebaceous glands.

The gel taught by Sibley et al. includes 1-3 weight/volume % salicylic acid, resorcitol or resorcitol monoacetate, sodium thiosulfate, α-aluminum oxide monohydrate, water, isopropanol and other ingredients, and is adjusted to a pH of 5.5 with sodium hydroxide. See, for instance, page 8 of the English language translation of Sibley et al. At least 85% of the α-aluminum oxide monohydrate particles have a particle size of at most 45 microns. Claim 1 of Sibley et al.

Sibley et al. provide no teaching regarding treatment of healed wounds or scars. Nor does the cited reference recognize or appreciate that inhibiting cyclooxygenase, directly or indirectly, improves the size and appearance of a scar. There is no disclosure in Sibley et al. regarding a method for improving the size and appearance of a healed wound that includes administering to an individual in need thereof a therapeutically effective amount of a cyclooxygenase inhibitor or of an NF-kB inhibitor, as is claimed by Applicant.

Therefore, Claims 1-4, 8, 11, 27-30, 34, 37 meet the requirements of 35 U.S.C.§ 102 (b) in view of Sibley et al.

II. Claims 1-4, 8, 11, 27-30, 34, 37 and 67-68 are rejected under 35 U.S.C. 102(b) as being anticipated by Singer (U.S. Patent No. 4,346,108).

The Examiner stated that the reference "discloses ibuprofen formulations for treatment of healed wound adhesions due to trauma." Office Action at page 6.

Applicant respectfully disagree.

Whereas Applicant's claimed invention is directed to a method for improving the size and appearance of a <u>healed</u> wound, Singer teaches systemic administration of a known compound, ibuprofen, "for preventing adhesion formation in humans or animals." Singer at Col. 1, lines 9-11. At Col. 1, lines 17-23, the reference defines adhesion as follows:

> Adhesion, i.e., scar tissue, forms following trauma to the tissue. This trauma is, most commonly, due to surgical intervention in the area, but can also be caused by infection or in response to the presence of a foreign body. The presence of scar tissue vis-a-vis

> normal tissue is undesirable and methods to prevent or lessen to [its] formation is desirable.

As further stated at Col. 3, lines 14-18, the reference discloses systemic administration of ibuprofen, its salts and esters for "preventing or diminishing the amount of adhesiveness that forms as a result of trauma surgery, infection or foreign bodies." Examples of surgical procedures discussed in the cited document include laparotomy, hysterectomy, caesarian section, or vasectomy.

At Col. 3, lines 29-35, Singer teaches that:

> Dosage of ibuprofen can commence, in the case of elective or scheduled surgery, 48 hours prior to surgery. Advantageous reduction or prevention or [of] adhesions can be obtained following trauma when administered after the healing process has begun, however it is preferable to administer the ibuprofen prior to the commencement of the healing process.

The cited reference does not address problems related to closed wounds and neither recognizes nor appreciates that a therapeutically effective amount of a cyclooxygenase inhibitor or of a NF-kB inhibitor can improve the size and appearance of such a wound. There is no disclosure or suggestion in Singer regarding a method for improving the size and appearance of a healed wound, that comprises administering to an individual in need thereof a therapeutically effective amount of a cyclooxygenase inhibitor or of an NF-kB inhibitor, as is claimed by Applicant.

Therefore, Claims 1-4, 8, 11, 27-30, 34, 37 meet the requirements of 35 U.S.C. 102(b) in view of Singer.

Claim Rejections Under 35 U.S.C. 103

I. Claims 1-4, 7-8, 10-11, 27-30, 33-34, 36-37, and 67-68 are rejected under 35 U.S.C. 103(a) as being unpatentable under Sibley et al. (DE 27 07 537).

The Examiner stated that the reference "discloses salicylic acid formulations for treatment of keloids caused by acne." The Examiner also stated that "[a]djustment of the amount of active [ingredient] would have been obvious to one skilled in the art at the time of the invention with the motivation of increasing or decreasing the amount of effect based upon the scar being treated." Office Action at page 7.

Sibley et al. teach a topical gel for controlling ongoing Acne vulgaris, prevention of blackheads and other conditions brought about by infected sebaceous glands. The gel disclosed in the cited document includes salicylic acid, resorcitol or resorcitol monoacetate, sodium thiosulfate, α-aluminum oxide monohydrate, water, isopropanol and other ingredients, and is adjusted to a pH of 5.5 with sodium hydroxide. See, for instance, page 8 of the English language translation of Sibley et al. At least 85% of the α-aluminum oxide monohydrate particles have a particle size of at most 45 microns. (Claim 1 of Sibley et al.)

As noted above, Applicant does not find the word "keloids" in the English translation of Sibley et al. The cited reference does not address problems relating to the size and appearance of healed wounds. There is no recognition or appreciation in the cited document that the size and appearance of a healed wound, such as a wound closed by regrowth of an epithelial barrier can be improved by administering a therapeutically effective amount of a cyclooxygenase or of a NF-kB inhibitor.

As seen, for example, at Col. 1, lines 21-23 of U.S. Patent No. 6,384,023 (attached as Exhibit A) salicylic acid generally is administered in acne for its keratolytic activity and for dissolving comedones thus helping to keep skin pores open in the presence of infection. Applicant respectfully submits that one skilled in the art, trying to improve the size and appearance of a healed wound, would not be motivated to apply salicylic acid to such a wound.

Thus, there is no disclosure, suggestion or motivation in Sibley et al. regarding a method for improving the size and appearance of a healed wound that includes administering to an individual in need thereof a therapeutically effective amount of a cyclooxygenase inhibitor or of an NF-kB inhibitor, as is claimed by Applicant.

Therefore, Claims 1-4, 7-8, 10-11, 27-30, 33-34, and 36-37 meet the requirements of 35 U.S.C. 103(a) over Sibley et al.

II. Claims 1-4, 7-8, 11, 27-30, 33-34, 37, and 67-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singer. (U.S. Patent No. 4,346,108)

The Examiner stated that the cited document "discloses ibuprofen formulations for treatment of healed wound adhesions due to trauma" and that "[a]djustment of the amount of active [ingredient] would have been obvious to one skilled in the art at the time of the invention with the motivation of increasing or decreasing the amount of effect based upon the scar being treated." Office Action at page 7.

As discussed above, Singer is related to systemic administration of ibuprofen, its salts or esters, for preventing the amount of adhesiveness that forms as a result of trauma surgery, infection or foreign bodies. As stated at Col. 3, lines 29-35, Singer recommends commencement of ibuprofen 48 hours prior to surgery.

The cited document provides no teaching or suggestion regarding improving the size and appearance of a healed wound. There is no recognition or appreciation in Singer that direct or indirect inhibition of cyclooxygenase can result to improving the size and appearance of a healed wound. Moreover, by recommending that ibuprofen administration be initiated prior to surgery, Singer, in fact, teaches away from Applicant's claimed invention.

Thus there is no disclosure, suggestion or motivation in Singer regarding a method for improving the size and appearance of a healed wound, which includes administering to an individual in need thereof a therapeutically effective amount of a cyclooxygenase inhibitor or of an NF-kB inhibitor, as is claimed by Applicant.

Therefore, Claims 1-4, 7-8, 11, 27-30, 33-34, and 37 meet the requirements of 35 U.S.C. 103(a) over Singer.

III. Claims 1-8, 10-14, 16-22, 25-34, 36-47, 50-51, 57-61, 67-74, and 77-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibley et al. (DE 27 07 537) in view of Lee (U.S. Patent No. 5,552,162).

The Examiner stated that Sibley et al. "is relied upon for all that it teaches as stated previously" and that the reference "does not teach combination of the formulation with a thermal insulating material." The Examiner also stated that Lee "teaches improvement of scar size and appearance with a thermal insulating material such as a hydrogel combined with a medicament."

Office Action at page 7. The Examiner further stated that it would have been obvious to one skilled in the art at the time of the invention to combine the references "with the motivation of providing a formulation having an additive scar reduction ability." Office Action at page 8.

As discussed above, Sibley et al. disclose treatment of ongoing acne and other conditions caused by inflammation of sebaceous glands. The reference neither discloses nor suggests a method of improving the size and appearance of a healed wound. There is no recognition or appreciation in Sibley et al. regarding inhibition, directly or indirectly of cyclooxygenase, nor does the cited reference disclose or suggest a method for improving the size and appearance of a healed wound, which includes administering to an individual in need thereof a therapeutically effective amount of a cyclooxygenase or NF-kB inhibitor.

Lee does not remedy the deficiencies of Sibley et al.

As discussed at Col. 6, lines 36-39, the reference discloses a thermal insulating material. Preferably the thermal insulating material contains a medicament that is a calcium antagonist, e.g., a calcium inhibitor, a protein kinase C inhibitor, or a calcium transport bolocker. At Col. 10, lines 44-55, for example, the reference states:

> A method of the present invention utilizes the discovery that calcium antagonists, which interfere with calcium metabolism or transport across the cell membrane, can inhibit exocytosis in fibroblast cells; can retard biosynthesis of collagen and sulfated glycosaminoglycans (GAG); can be used to decrease the collagen content of the extracellular matrix; and can also stimulate increased collagenase activity, leading to softening of the scar tissue. These features work together to control wound scar production; by minimizing, preventing or reversing the scarring process, depending upon the course of the disease or type of wound treated.

As with Sibley et al., there is no disclosure or suggestion in Lee regarding inhibiting cyclooxygenase, directly or indirectly, nor regarding administration of an effective amount of a cyclooxygenase (or NF-kB) inhibitor to improve the size and appearance of a healed wound.

Thus neither reference, alone or in combination, discloses or suggests Applicant's claimed method for improving the size and appearance of a healed wound, comprising

administering to an individual in need thereof a therapeutically effective amount of a cycooxygenase inhibitor or of a NF-kB inhibitor.

Therefore, Claims 1-8, 10-14, 16-22, 25-34, 36-47, 50-51, 57-61, 69-74, and 77-78 meet the requirements of 35 U.S.C. 103(a) over Sibley in view of Lee.

IV. Claims 23-24 and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable under Sibley et al. (DE 27 07 537) in combination with Lee (U.S. Patent No. 5,552,162) and further in combination with Allen (U.S. Patent No. 4,895,727).

The Examiner stated that Sibley et al. and Lee are relied upon for all that they teach as stated previously and that "[n]either reference teaches inclusion of a deodorant agent such as aluminum zirconium trichlorohydrex or zinc acetate." The Examiner stated that Allen "is relied upon for teaching that zinc acetate increases the penetration of salicylic acid." The Examiner further stated that "it would have been obvious to one skilled in the art at the time of the invention to include zinc acetate in the combined formulation of Lee and Allen with the motivation of increasing the penetration of salicylic acid through the skin." Office Action at page 8.

As stated above, neither Sibley et al., nor Lee, alone or in combination, disclose or suggest Applicant's claimed invention. Allen does not remedy the deficiencies of Sibley or Lee.

Allen discloses a method for inducing a reservoir effect in skin and mucous membranes so as to enhance penetration and retention of topically applied pharmacologically active therapeutic and cosmetic agents therein. Allen at Col. 1, line 65 to Col 2, line 1.

There is no disclosure or suggestion in Allen regarding a method for improving the size and appearance of a healed wound that includes administering to an individual in need thereof a therapeutically effective amount of a cyclooxygenase inhibitor.

Thus none of the cited references, alone or in combination discloses or suggests Applicant's claimed invention.

Therefore, Claims 23-24 and 48-49 meet the requirements of 35 U.S.C. 103(a) over Sibley et al. in combination with Lee and further in combination with Allen.

V. Claims 9 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sibley et al. (DE 27 07 537) in view of Boghosian, et al. (U.S. Patent No. 4,244,948).

The Examiner stated that Sibley et al. "is relied upon for all that it teaches as stated previously" and that the reference "does not teach the acetylsalicylic esters of instant Claim 9 and 35. The Examiner also stated that Boghosian, et al. "is relied upon for teaching that acetylsalicylic esters retain the anti-inflammatory properties of acetylsalicylic acid and that the acetylsalicylic esters penetrate the skin more readily with decreased irritation to the skin than acetylsalicylic acid." The Examiner further stated that "it would have been obvious to one skilled in the art at the time of the invention to substitute acetylsalicylic esters with the motivation of providing a form having increased penetration to the skin with decreased irritation." Office Action at page 9.

As discussed above, Sibley et al. neither disclose nor suggest Applicant's claimed invention. Boghosian et al. "relates to a method for topically treating inflammation in humans or animals." More specifically, the reference discloses compositions useful for treating acne. At Col. 2, lines 36-41, Boghosian et al. states that:

> the term "treatment of acne" is used to mean the temporary alleviation of the inflammation of the affected skin and other signs and symptioms associated with acne.

The cited reference does not addressed the problems associated with healed wounds, nor does it recognize or appreciate that direct or indirect inhibition of cyclooxygenase can result in improvement in the size and appearance of a healed wound. As with Sibley et al., there is no disclosure or suggestion in Boghosian et al. regarding a method for improving the size and appearance of healed wounds comprising administering to an individual in need thereof a therapeutically effective amount of a cyclooxygenase inhibitor or of a NF-kB inhibitor. Thus neither reference, alone or in combination, discloses or suggests Applicant's claimed invention.

Therefore, Claims 9 and 35 meet the requirements of 35 U.S.C. 103(a) over Sibley et al in view of Boghosian et al.

INFORMATION DISCLOSURE STATEMENT

Applicant has filed an Information Disclosure Statement on August 17, 2001. The filing of the Information Disclosure Statement is acknowledged at page 2 of the Office Action. A copy of the PTO Form 1449, initialed by the Examiner, is respectfully requested.

In addition, a Second Supplemental Information Disclosure Statement is filed concurrently herewith. Entry of the Second Supplemental Information Disclosure Statement is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: June 18, 2003

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

At pages 1 and 45, replace the title of the application with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the title:

METHODS FOR IMPROVING SIZE AND APPEARANCE OF A HEALED WOUND

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

67. (Amended) [Use, for the manufacture of a medicament] A method for preventing or treating a condition caused by the appearance of a hypertrophic or a keloid scar on a healed wound, comprising administering to an individual in need thereof a therapeutically [of an] effective amount of a cyclooxygenase inhibitor, in combination with a substance that relieves skin irritation, an antimicrobial agent, and a thermal insulating material.

68. (Amended) [Use, for the manufacture of a medicament] A method for preventing or treating a condition caused by the appearance of a hypertrophic or a keloid scar on a healed wound, comprising administering to an individual in need thereof a therapeutically [of an] effective amount of an NF-kB inhibitor, in combination with a substance that relieves skin irritation, an antimicrobial agent, and a thermal insulating material.